

Remarks

Introduction

The claims have been amended. Claims 5 and 21 have been amended to more clearly set forth the subject matter of the invention. Claims 27, 5-6, and 20-26 are currently pending. Claim 27 is the sole independent claim.

Section 112 rejections

Claim 5

Claim 5 has been rejected under 35 U.S.C. §112, second paragraph as indefinite. The Examiner has stated that claim 5 lacks antecedent basis by including wherein the substituent on J may include unsubstituted alkyl. Claim 5 has been amended to delete the unsubstituted alkyl substituent. Therefore, reconsideration and withdrawal of the rejection of claim 5 under Section 112, second paragraph is respectfully requested.

Claims 23-25, 26, and 28

Claims 23-25, 26, and 28 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that “the specification, while being enabling for the treatment of Alzheimer’s disease does not reasonably provide enablement for the prevention of Alzheimer’s disease or the treatment of any other disease applicant considers mediated by the inhibition of cellular production of amyloid B.” This rejection is respectfully traversed.

Alzheimer’s disease is characterized by the presence of “plaques” formed by an accumulation of Amyloid beta protein. The Examiner has stated that the methods of the present invention, which include the administration of the compounds of the present invention having inhibitory activity for amyloid beta precursor protein are enabled by the specification for the treatment of Alzheimer’s. However, the Examiner has alleged that prevention of Alzheimer’s by the same methods, as in claim 25, is not enabled. Similarly, methods of treatment or prevention

of other diseases associated with the accumulation of amyloid beta protein have been alleged not to be enabled by the Examiner. Applicants respectfully traverse.

Alzheimer's disease and other conditions such as Down syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch), and inclusion type myositis are all disease conditions characterized by the accumulation of amyloid beta protein. The fact that these diseases are caused by the presence of excessive amounts of amyloid beta protein are well-known and documented in the art. Examples of literature pointing out the relationship between amyloid beta protein and each of these conditions are attached. The attached E-medicine article lists in Table 1, several amyloidosis conditions at page 3. Jacobson, Daniel R. MD., "Amyloidosis, Overview." Similarly, "Life Force Hospitals Amyloidosis" lists amyloid beta related conditions in Table 2, beginning on Page 2. "Today@UCI" points out on page 2, first full paragraph, that "A small protein called beta-amyloid accumulates pathologically in both Alzheimer's disease and inclusion body myositis." Each of these articles is indicative of the plethora of information available showing the many diseases associated with and caused by amyloid beta.

Each of the disease conditions described above results from the accumulation of amyloid beta protein. The Examiner has accepted the present invention is enabled for the treatment of Alzheimer's disease since the compounds of the present invention have been found to inhibit formation and accumulation of amyloid beta protein. Applicants respectfully submit that, following the same logic, the compounds of the present invention are also enabled for prevention of Alzheimer's disease since that preventing the formation of amyloid beta protein would prevent the formation of the amyloid beta plaques which has been recognized by those skilled in the art as a cause of Alzheimer's. Therefore, Applicants respectfully submit that the present invention is enabled for the treatment as well as prevention of Alzheimer's disease.

As described above and in the attached literature, several disease conditions are caused by formation and deposition of amyloid beta protein. These include, as set forth in claim 24, amyloid angiopathy, cerebral amyloid angiopathy, systemic amyloidosis, Alzheimer's disease,

hereditary cerebral hemorrhage with amyloidosis of the Dutch type, inclusion body myositis, and Down's syndrome. Similar to Alzheimer's Disease, each of these conditions is caused by accumulation of amyloid beta protein. Since the methods of the present invention are effective in inhibiting the formation of amyloid beta protein, applicants respectfully submit that the present invention is enabled for the prevention and treatment of Alzheimer's disease as well as any other disease characterized by the accumulation of amyloid beta protein.

Therefore reconsideration and withdrawal of the rejection of claim 23-26 and 28 are appropriate and respectfully requested.

Claims 21, 22 and 28

Claims 21, 22, and 28 have been "rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the inhibition of proteolytic cleavage of amyloid beta precursor protein does not reasonably provide enablement for the modulating of the level of amyloid beta precursor protein.

Claim 21 has been amended to a method of inhibiting production of Amyloid Beta Protein and claim 28 has been amended to a method of inhibiting proteolytic cleavage of Amyloid Beta Precursor Protein (APP). Since the Examiner has indicated that a method of inhibition of proteolytic cleavage of amyloid beta precursor protein is enabled, which prevents the formation of Amyloid Beta Protein, Applicants respectfully submit that claims 21 and 28 as amended and claim 22, which depends from claim 21, are allowable. Therefore, reconsideration and withdrawal of the rejection of claims 21, 22, and 28 are respectfully requested.

Section 102 Rejections

Claims 27, 5 and 20

Independent claim 27 and dependent claims 5 and 20 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Linfield. et al. The Examiner asserts that compound 105 on page 1743 of Linfield includes substituents corresponding to the present invention as

follows: wherein D is hydrogen, E is phenyl substituted with halogen (chlorine), G is phenyl substituted with a halogen (chlorine) and J is phenyl substituted with alkyl substituted alkyl (n-propyl). This rejection is respectfully traversed.

The Examiner has alleged that phenyl substituent on J meets the claim language, "substituted alkyl." Specifically, the Examiner asserts that n-propyl, a straight chain three carbon chain, is a substituted alkyl. Applicants respectfully submit that not only would no person of skill in the art consider n-propyl to be a substituted moiety, but also, n-propyl is not within the definition of n-propyl set forth in the present specification. Therefore, compound 105 of Linfield is not within the scope of independent claim 27.

Claim 27 was amended in the response dated January 16, 2004 to exclude unsubstituted alkyl as a substituent on the phenyl group of J. This amendment specifically excluded n-propyl, which is within the definition of unsubstituted alkyl in the specification. Alkyl is defined at page 3, line 27, of the specification as "straight or branched chain alkyl radicals having in the range of about 1 up to 12 carbon atoms." A substituted alkyl is defined as "an alkyl radical further bearing one or more substituents such as cycloalkyl, cycloalkenyl, aryl, heterocycle optionally having one or more double bonds, halogen, alkoxy, cyano, cyanomethyl, nitro, amino, amide, amidine, hydroxy, carboxyl, carbamate, ether, ester, sulfonyl, sulfonamide, mercapto, and the like." Clearly, the substituent must be something other than alkyl. An "alkyl substituted alkyl" as described by the Examiner would merely be an alkyl.

The state of the art reflects the Applicants choice of describing the substituents as in the present invention. One clear example in the art is IUPAC rules of nomenclature, a copy of which is attached. As set forth in the rules, the first step in naming a chemical structure is identifying the parent structure. Pentane is provided as an example of a parent structure. An example of an unsubstituted alkyl within the meaning of the present invention would be a pentane radical.

The IUPAC rules point out that some structures may be named in several ways in Table 1, also attached. However, the Examiner will appreciate that 1) the alternative naming is only used when additional functional groups such as ether, ketone, carboxylic acid, etc. are included and 2) there are a finite number of suitable names. For example, an appropriate name for a particular propane ether may be 1-Ethoxypropane or Ethyl propyl ether. However, this compound will not be properly referred to as 1-ethoxy-2-methyl-ethane or as ethyl methylethyl ether, which seem to be the substituent names as proposed by the Examiner considering that the Examiner has stated that propyl is an alkyl substituted alkyl.

Since propyl falls within the definition of alkyl as set forth in the present invention by the Applicants and is recognized by those skilled in the art and under the nomenclature guidelines NOT to be a substituted radical, Applicants respectfully submit that compound 105 does not anticipate claim 27 of the present invention. Therefore, reconsideration and withdrawal of the rejections under Section 102 are appropriate and respectfully requested.

Section 103 Rejections

Claims 27, 5-6, and 20

Claims 27, 5-6, and 20 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Linfield et al. ("Linfield"). The Examiner stated at page 15 of the Office Action dated August 16, 2004 that Linfield "does not disclose a species corresponding to the instant invention wherein D is hydrogen, E is phenyl substituted with halogen (chlorine), G is phenyl substituted with a halogen (chlorine) and J is phenyl substituted with methyl or halogen." The Examiner continues to allege that, "it would have been obvious to one of ordinary skill in the art when faced with Linfield et al. to prepare compounds of the instant invention wherein J is methyl or halogen." This rejection is respectfully traversed on the grounds that the Examiner has failed to establish a *prima facie* case of obviousness.

In order to establish a *prima facie* case of obviousness, there must be (1) some teaching or suggestion to modify a reference, (2) a reasonable expectation of success, and (3) all of the

limitations of the claims must be taught or suggested by the reference. The Examiner asserts at page 16 of the Office Action that "the motivation would stem from the desire to prepare other useful substituted sulfonanilides as antibacterial agents." However, no such teaching is present in Linfield, which in fact teaches away from the compounds of the present invention.

Linfield is a study of the antibacterial activity of certain substituted anilides of carboxylic and sulfonic acids. In the study, three structurally distinct carboxylic acids and one sulfonic acid were examined. Two of the sulfonic acid derivatives (compounds 104 and 105) were added to the study to confirm the findings of earlier research by Charles and Weller. See footnote 9. These are the only two compounds in the study wherein Linfield's "R" group, which the Examiner has alleged corresponds to the "-CHDG" group of the present invention, is not hydrogen, which is of paramount significance considering that Linfield "confirmed [Charles and Weller's] observation that replacement of the sulfonamide proton by an alkyl group destroyed [antibacterial] activity." Page 1744 second column, line 7. Since the only motivation in Linfield would be to prepare antibacterially active compounds and any compound having R other than hydrogen would not have that activity, Linfield fails to suggest preparing compounds as in the present invention and in fact teaches away from the present invention, wherein "-CHDG" will never be hydrogen.

Since Linfield fails as a proper reference under Section 103, reconsideration and withdrawal of the rejections under Section 103 are appropriate and respectfully requested.

In view of the amendments and remarks set forth above, reconsideration and withdrawal of the rejections are appropriate and respectfully requested. Applicants submit the present claims are patentably distinct over the art and allowable in form. Early allowance is therefore solicited. The Examiner is encouraged to contact the undersigned attorney should there be any questions regarding this amendment.

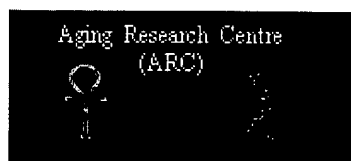
Applicant: Smith et al.
Application No: 09/890,927
Docket No: 1188-67 PCT/US
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Respectfully submitted,

A handwritten signature in black ink, appearing to read "Christina L. Warrick". The signature is fluid and cursive, with the first name "Christina" being more prominent and the last name "Warrick" following in a similar style.

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Caffeine stimulates amyloid beta-peptide release from beta-amyloid precursor protein-transfected HEK293 cells.

- Querfurth HW, Jiang J, Geiger JD, Selkoe DJ

J Neurochem 1997 Oct;69(4):1580-91.

Extracellular amyloid beta-peptide (A beta) deposition is a pathological feature of Alzheimer's disease and the aging brain. Intracellular A beta accumulation is observed in the human muscle disease, inclusion body myositis. A beta has been reported to be toxic to neurons through disruption of normal calcium homeostasis. The pathogenic role of A beta in inclusion body myositis is not as clear. Elevation of intracellular calcium following application of calcium ionophore increases the generation of A beta from its precursor protein (betaAPP). A receptor-based mechanism for the increase in A beta production has not been reported to our knowledge. Here, we use caffeine to stimulate ryanodine receptor (RyR)-regulated intracellular calcium release channels and show that internal calcium stores also participate in the genesis of A beta. In cultured HEK293 cells transfected with betaAPP cDNA, caffeine (5-10 mM) significantly increased the release of A beta fourfold compared with control. These actions of caffeine were saturable, modulated by ryanodine, and inhibited by the RyR antagonists ruthenium red and procaïne. The calcium reuptake inhibitors thapsigargin and cyclopiazonic acid potentiated caffeine-stimulated A beta release. NH₄Cl and monensin, agents that alter acidic gradients in intracellular vesicles, abolished both the caffeine and ionophore effects. Immunocytochemical studies showed some correspondence between the distribution patterns of RyR and cellular betaAPP immunoreactivities. The relevance of these findings to Alzheimer's disease and inclusion body myositis is discussed.

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Amyloidosis

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General Considerations

(Note: Amyloid can be studied in the context of cell injury or immunological diseases. For this reason, we have included the same material in both Cell Injury and Immunopathology.)

Amyloidosis is not a single disease entity but rather a diverse group of disease processes characterized by extracellular tissue deposits, in one or many organs, of protein materials which are generically termed amyloid. Amyloid is distinguished grossly by a starch-like staining reaction with iodine (thus the term amyloid), microscopically by its extracellular distribution and tinctorial and optical properties when stained with Congo red, and by its protein fibril structure as shown by electron microscopy and x-ray crystallography (see Table-1).

Table-1

Characteristics of Amyloid

Homogeneous pink "soft, fluffy, or smudgy" extracellular material in tissue sections stained with H&E

Orange color by light microscopy and green birefringence by polarizing microscopy in sections stained with Congo red

Fine nonbranching fibrils, 7.5-10 nm in diameter, in thin sections by electron microscopy

"Beta-pleated" sheet structure of fibrils by x-ray diffraction

(Adapted from Cohen, A.S. and Skinner, M, New Engl. J. Med., 323:542-543, 1990)

Amyloid deposition may be either a primary (idiopathic) process without known antecedent or secondary to some other condition and may be localized to one specific site or generalized throughout the body (systemic), usually with fatal consequences. Although considerable overlap is seen in the organ distribution of various forms of amyloid, primary amyloidosis tends to involve mesodermal tissues, most frequently affecting peripheral nerves, skin, tongue, joints, heart, and liver while secondary amyloidosis mainly affects parenchymatous organs, such as spleen, kidneys, liver, and adrenals.

Amyloid deposits typically contain three components. Amyloid protein fibrils account for about 90% of the amyloid material and comprise one of several different types of proteins with the capacity to fold into what are called "beta-pleated" sheet fibrils, a unique protein configuration with binding sites for Congo red. In addition, amyloid deposits are intimately associated with the amyloid P (pentagonal) component (AP), a glycoprotein related to normal serum amyloid P (SAP), and are closely associated with sulfated glycosaminoglycans (GAG), complex carbohydrates of connective tissue.

Systemic forms of amyloid are derived from circulating protein precursors by conversion from soluble into insoluble (fibrillar) form. By convention, amyloid fibril types are designated by two letters: A for amyloid followed by a letter for the chemical type. There are two, chemically distinct, major types of amyloid protein fibrils designated AL and AA, respectively, and several minor types unrelated to AL or AA. AL (amyloid light chain) fibrils associated mainly with multiple myeloma are related to monoclonal immunoglobulin light chains synthesized by abnormal plasma cells. AA fibrils associated mainly with chronic inflammatory diseases are related to the nonimmunoglobulin amyloid associated (AA) protein and its serum precursor (SAA), an acute phase reactant synthesized by liver cells.

Classification

The classification of amyloidosis is based upon the tissue distribution of amyloid deposits (local or systemic amyloidosis), the absence or presence of preexisting disease (primary or secondary amyloidosis), and the chemical type of amyloid protein fibril (see Table-2).

Table-2

Classifications of Amyloidosis

Clinical Classification	Associated Condition	Amyloid Fibril Type	Precursor
<hr/>			
<u>Systemic Amyloidosis</u>			
Primary or Secondary	Multiple myeloma	AL	Iglambda (or kappa chains)

	Chronic inflammatory disease		
Secondary	__ Rheumatoid arthritis	AA	SAA
	__ Tuberculosis		
	__ Skin and lung abscesses		
Secondary	Cancer	AA	SAA
	Hodgkin's disease		
Secondary	Hemodialysis for CRF(*)	beta2-m(**)	beta2-m
	Heredofamilial amyloidosis		
	__ Familial	AA	SAA
Primary	Mediterranean		
	__ Fever		
	__ Familial amyloid	Transthyretin	Transthyretin (#)
	__ polyneuropathy		

Localized Amyloidosis

Senile cardiac amyloidosis	Transthyretin	Transthyretin
Senile cerebral amyloidosis:		
__ Alzheimer's disease	Amyloid beta protein	Amyloid precursor protein (APP)
Endocrine tumors		
__ Medullary carcinoma	Procalcitonin	Calcitonin
__ of thyroid		

(*): chronic renal failure; (**): beta2-microglobulin is a normal serum protein and a component of MHC class I molecules; (#): transthyretin is a normal serum protein that transports thyroxine and retinol (vitamin A) and is deposited in a variant form.

Amyloidosis Related to Monoclonal Ig Light Chains. AL amyloid is derived from monoclonal Ig light chains, usually of lambda type, produced by abnormal clones of Ig-secreting plasma cells (B cells). AL type of amyloidosis may be primary or may occur secondary to multiple myeloma or some other monoclonal gammopathy (immunocyte dyscrasia). It is the most common type of amyloidosis seen in the U.S.

today.

AL type of amyloidosis occurs in about 5-10% of patients who have preexisting or coexisting multiple myeloma. Multiple myeloma is seen mainly in patients over 40 years of age (median age of 60 years) and, next to metastatic carcinoma, is the most common malignant tumor of bone. It is a malignant tumor of plasma cells which arises in the bone marrow, permeates the medullary cavity, erodes the bone cortex, and is characterized by multiple osteolytic ("punched out") lesions of vertebrae, skull, ribs, pelvis, and other bones and by narrow-banded electrophoretic peaks of monoclonal IgG (less commonly IgA, rarely IgD or IgE) in the serum and free light chains of the same kappa or lambda type in the urine (Bence-Jones proteinuria). An identical, patient-specific, free monoclonal light chain protein is also usually present in myeloma serum but, being smaller than albumin molecules, readily passes into the urine. Overall, about 70% of myeloma patients have both serum monoclonal Ig and urinary light chains, and the remaining patients have urinary light chains alone without serum monoclonal Ig.

The AL fibrils are derived from circulating light chains by proteolytic cleavage and conversion to an insoluble form. The organ distribution of AL deposits is usually generalized (systemic) and conforms to either the primary or secondary patterns previously noted.

AL type of amyloidosis is also associated with some other rare monoclonal gammopathies (plasma cell/B immunocyte dyscrasias), such as solitary myeloma (of bone or soft tissue), Waldenstrom's macroglobulinemia, or heavy chain disease in which there are also sometimes an increased production of free light chains that become deposited as amyloid.

Noteworthy, the majority of patients who develop AL type of amyloidosis apparently do so in the absence of clinically overt myeloma or other predisposing disease, and such cases are commonly referred to as primary or idiopathic amyloidosis. Nevertheless, in long term follow up, a substantial proportion of these patients do manifest overt, monoclonal Ig-producing plasma cell or lymphoid cell dyscrasias, such as myeloma, macroglobulinemia, or lymphoma.

Amyloidosis Associated with Inflammatory or Infectious Diseases. The amyloid deposits in this form of amyloidosis have a systemic distribution and contain AA (amyloid-associated) fibrils which are related to the nonimmunoglobulin AA protein and its serum protein precursor (SAA), an acute phase reactant synthesized by hepatic cells. Also called reactive or secondary amyloidosis, this form of amyloidosis occurs mainly as a complication of long standing inflammatory diseases, most frequently rheumatoid arthritis (A 5-10% of rheumatoid

patients) and also dermatomyositis, scleroderma, regional enteritis, and ulcerative colitis.

Prior to the antibiotic era, chronic tissue-destructive infectious diseases, such as tuberculosis, chronic osteomyelitis, and bronchiectasis, were the most common antecedents of secondary amyloidosis. Now, amyloidosis often develops as a complication of skin and lung abscesses occurring in subcutaneous heroin abusers.

Reactive-type amyloidosis may also occur in association with cancer, such as Hodgkin's disease and renal cell carcinoma.

Other Amyloids and Disease Associations.

1. Amyloid associated with hemodialysis (AH). The systemic amyloid deposition of beta2-microglobulin (beta2-m), a normal serum protein, occurs as a complication of long-term dialysis in patients with chronic renal failure because this protein does not pass through conventional dialysis membranes.
2. Amyloid associated with familial Mediterranean fever. The systemic deposition of AA fibrils occurs in familial Mediterranean fever, an autosomal recessive disorder seen in individuals of Sephardic Jewish, Armenian, and Arabic descent.
3. Amyloid associated with familial amyloid neuropathies (AF). Amyloid deposition of a mutant form of transthyretin, a normal serum protein that transports thyroxine and retinol (vitamin A), occurs in peripheral nerves in familial amyloid polyneuropathy, an autosomal dominant disorder occurring in different parts of the world (Sweden, Portugal, Japan, and the U.S.).
4. Localized deposits of amyloid.

Endocrine-related. Localized amyloid deposits are associated with hormones produced by certain endocrine tumors and endocrine glands, such as medullary carcinoma of the thyroid gland (procalcitonin), islet cell tumors of the pancreas, and the islets of Langerhans (islet associated polypeptide, IAPP) in patients with type II diabetes mellitus.

Age-related. Amyloid deposits of transthyretin occur in the heart of elderly patients with senile cardiac amyloidosis. Beta amyloid protein is deposited in the cerebral blood vessels and plaques of patients with senile cerebral amyloidosis and Alzheimer's disease.

Pathogenesis of Amyloidosis

Amyloidosis is not one disease but a diverse group of diseases of acquired or hereditary origin and characterized by the extracellular deposition of one of several different types of protein fibrils with similar properties and called amyloid. Despite their biochemical diversity, amyloid proteins share unique features: fibril ultrastructure, cross beta x-ray diffraction pattern, and staining characteristics (with Congo red).

The mechanisms of amyloid formation, although not well understood, can be summarized as follows:

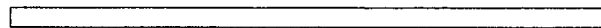
- each type of amyloid is derived from a serum precursor protein (see Table 2);
- with common forms of amyloid disease, some stimulus or key process increases the concentration of the serum precursor protein, e.g., free Ig light chains in AL amyloid associated with myeloma; the acute phase reactant SAA in AA amyloid associated with inflammation or familial Mediterranean fever; and beta2-macroglobulin in AH amyloid associated with chronic renal failure and hemodialysis;
- with familial forms of amyloid disease, the primary structure of the serum precursor protein is genetically altered, e.g., mutant transthyretin in AF amyloid associated with familial polyneuropathy; mutant beta protein in amyloid associated with familial Alzheimer's disease;
- with AL and AA amyloid, the serum precursor proteins are apparently processed by partial degradation to produce amyloid fibrils, in as much as the amyloid proteins isolated from AL and AA fibrils are usually smaller than the precursor proteins ; furthermore, AL and AA fibrils can be produced from the precursor proteins in vitro by partial proteolysis;
- SAA, the serum precursor protein of AA amyloid associated with chronic inflammation, is an acute phase reactant (a generic term for a group of plasma proteins whose levels increase greatly in inflammatory conditions) and is synthesized and secreted by hepatocytes under stimulation by interleukin-1 (IL-1) released from activated macrophages;
- systemic deposits of amyloid fibrils are intimately associated with the amyloid P component (AP), a glycoprotein related to normal serum amyloid P (SAP) which is an evolutionary conserved protein, and with sulfated glycosaminoglycans (GAG), complex carbohydrates of connective tissue.

Figure 3 - Formation and deposition of AL and AA amyloid.

Some Clinical and Laboratory Manifestations of Amyloidosis

Involvement:	Manifestations:
Kidney	Proteinuria, nephrotic syndrome, renal failure
Heart	Congestive failure, cardiomegaly
Gastrointestinal tract	Macroglossia, obstruction, malabsorption
Liver, spleen	Hepatomegaly, splenomegaly
Skin	Waxy papules
Bone marrow	Plasmacytosis/multiple myeloma
Serum and urine	Monoclonal Ig and light chains

Pathology



Systemic amyloidosis (AA) related to chronic inflammation tends to involve parenchymatous organs, such as kidneys, spleen, liver, and adrenals, while amyloidosis (AL) related to myeloma tends to affect mesodermal or other tissues, such as heart, gastrointestinal tract, peripheral nerves, skin, and tongue. Nevertheless, the overlap in organ involvement is such that the different forms of systemic amyloidosis are not distinguishable on that basis alone.

Grossly, organs extensively infiltrated by amyloid are usually enlarged and have a pale, waxy ("lardaceous") or varnished appearance and tough consistency. The iodine test for amyloid is done by applying iodine solution to the washed cut surface of the organ: amyloid typically stains mahogany-brown, and this color reaction changes to blue (a "starch-like" reaction) after the application of dilute sulfuric acid.



Amyloidosis of the left atrial endocardium.



Cross section of amyloid myocardium stained with Lugol's iodine solution.

The staining reactions of amyloid reflect its complex composition. Amyloid deposits in tissues typically stain as follows: homogeneously pink (as do other eosinophilic hyaline materials) with H&E; metachromatically (as do sulfated glycosaminoglycans) with crystal violet and similar dyes; and positively (as do glycoproteins) with periodic acid-Schiff. A diagnostic criterion, amyloid stains pink or orange with Congo red and, further, with Congo red staining shows green birefringence by polarizing microscopy, specific and unique properties shared by all amyloids due to their beta-pleated fibrillar structure.



Amyloid deposition (green birefringence) in tongue. Congo red. Polarizing microscopy.

Legend Structure of an amyloid fibril, depicting the beta-pleated sheet structure and binding sites for the Congo red dye, which is used for diagnosis of amyloidosis.

The distribution of amyloid deposits is extracellular, closely related to the connective tissue framework of involved organs, and often interposed between parenchymal cells and their blood supply.

Kidneys. Grossly, amyloid kidneys are usually enlarged, pale, and smooth surfaced and have a tough consistency. On cortical transection, the glomeruli (barely visible as pink dots in the normal kidney) may be seen as enlarged, waxy, gray dots.



Primary amyloidosis of kidneys.

Histologically, the mesangium and capillary basement membrane of glomeruli are the most frequent renal sites of amyloid deposition, followed by involvement of arteriolar and arterial walls and peritubular interstitial tissues. As the extent of the amyloid deposition increases, the glomerular capillary tufts become obliterated and replaced by functionless spherical masses of amyloid material



Amyloidosis of kidney. Most of this glomerulus is the site of homogeneous pink "soft fluffy" deposits of amyloid located focally in the widened mesangial regions and in the thickened capillary basement membranes. H&E.



Amyloidosis of kidney. This photomicrograph taken with plane polarized light shows diffuse amyloid deposition (green birefringence) in the glomerular tufts throughout the mesangial regions. Congo red. Polarizing microscopy.



Amyloidosis of kidney. Congo red - polarizing microscopy.



Amyloidosis of kidney. In this photomicrograph, the glomerulus shows diffuse amyloid deposition in the widened mesangial, or intercapillary, regions and in the thickened capillary basement membranes. Glomerular capillary lumens are narrowed by concentric and eccentric deposits of amyloid material. PASH



Amyloidosis of kidney. As the amyloid deposition continues, the glomerular tufts become obliterated and replaced by spherical masses of amyloid material. H&E.

By electron microscopy, the first deposition of amyloid fibrils in the kidney is seen on the endothelial side of the glomerular capillary basement membrane (subendothelial deposits).

Liver. The amyloid liver is usually grossly enlarged, pale, smooth surfaced, and firm and, when sectioned, has sharp rigid edges.

Microscopically, amyloid is initially deposited in the spaces (of Disse) between the hepatocytes and vascular sinusoids. As more amyloid accumulates, it compresses the hepatic cords and sinusoids. The hepatic cords undergo nutritional and pressure atrophy and become displaced or replaced by bands and nodules of amyloid.



Amyloidosis of liver. The hepatic cords are diminished in size and are compressed, fragmented, and replaced by amyloid deposition (pink). H&E.



Amyloidosis of liver. The hepatic parenchyma is infiltrated and replaced by nodular accumulations of amyloid (pink) in which remnants of hepatic cords are seen. H&E.

Spleen. Amyloidosis of the spleen has two different anatomical patterns. Most commonly, the amyloid deposition is limited to the splenic follicles, resulting in the gross appearance of a moderately enlarged spleen dotted with gray nodules (so called "sago" spleen). Alternatively, the amyloid deposits may spare the follicles and mainly infiltrate the red pulp sinuses, producing a large, firm spleen mottled with waxy discolorations ("lardaceous" spleen).



Amyloidosis of the spleen

Heart. Amyloidosis of the heart may accompany systemic amyloid deposition or localized organ involvement (amyloidosis of aging). Histologically, the deposits are located between the myocardial fibers or in the walls of the coronary arteries



Amyloidosis of heart. Amyloid infiltrates the muscular wall of a coronary artery. Congo red.

Other Organs. Amyloid deposition may involve the adrenals, thyroid,

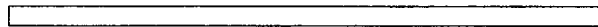
skin, tongue, and other portions of the alimentary tract. In the adrenals, extracellular amyloid deposits encompass, compress, and replace the cortical cells. A comparable pattern of amyloid deposition is seen in the thyroid. The alimentary tract may be involved at any level, from the tongue to the rectum (submucosa).



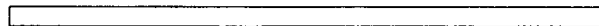
Amyloidosis of adrenal gland. Amyloid deposits surround, compress, and replace some cortical cells and infiltrate the wall of a small blood vessel (at one corner of the photomicrograph). Congo red.



Amyloidosis of tongue (interstitial tissue). Amyloid infiltrates the capillary walls and narrows the lumens of some of them. H&E.



Clinical Aspects



The clinical manifestations of amyloidosis vary from minimal to life threatening, depending upon the organs involved (see Table-3).

Table-3

Some Clinical and Laboratory Manifestations of Amyloidosis

Involvement:	Manifestations:
Kidney	Proteinuria, nephrotic syndrome, renal failure
Heart	Congestive failure, cardiomegaly
Gastrointestinal tract	Macroglossia, obstruction, malabsorption
Liver, spleen	Hepatomegaly, splenomegaly
Skin	Waxy papules
Bone marrow	Plasmacytosis/multiple myeloma
Serum and urine	Monoclonal Ig and light chains

The clinical standard for the diagnosis of amyloidosis is a tissue biopsy. Common biopsy sites include: gingiva, rectum (submucosa), subcutaneous fat-pad tissue, skin, and specific organs, such as kidney and liver.

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UCI team creates first live research model that shows common degenerative muscle disease

Breakthrough discovery offers research hope for form of myositis and possibly Alzheimer's disease

Irvine, Calif., April 22, 2002

A UC Irvine research team has derived the first animal model that exhibits the pathological and behavioral symptoms of inclusion body myositis, the most common degenerative muscle disease among the elderly. The ability to study this form of myositis in live tissue may lead to significant research breakthroughs on this poorly understood and presently incurable ailment.

The effort, led by UCI neurobiologists Frank LaFerla and Michael Sugarman, also holds promise for further advances in research on Alzheimer's disease, the leading cause of dementia in the United States, which shares similar molecular processes with inclusion body myositis. The findings appear in the April 23, 2002, issue of *Proceedings of the National Academy of Sciences*.

"These mice are valuable because they allow us to evaluate the therapeutic compounds that can halt or reverse the disease, something that previously could not be done," said LaFerla, associate professor of neurobiology and behavior. "Also, because myositis is so closely linked with Alzheimer's disease, this mouse model presents a great opportunity to study the molecular mechanisms that are common to both degenerative disorders in living tissue."

The UCI research focuses on inclusion body myositis, a form of

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the disease that causes damage to muscle fibers and ultimately leads to loss of muscle tissue, particularly in the limbs. Inclusion body myositis is a relatively new disorder that was first recognized in the early 1970s. It has been historically misdiagnosed, so it is difficult to determine the exact number of affected individuals, although it is regarded as the most common degenerative muscle disease in older Americans.

A small protein called beta-amyloid accumulates pathologically in both Alzheimer's disease and inclusion body myositis. What triggers its accumulation is unclear, although it is well-established that beta-amyloid is derived from a larger parental entity called the beta-amyloid precursor protein. LaFerla and Sugarman created genetically modified mice that produced large quantities of the beta-amyloid precursor molecule selectively in skeletal muscle cells. These researchers showed that abnormally high levels of this protein cause degeneration of muscle tissue leading to the motor-behavioral difficulties associated with inclusion body myositis.

In Alzheimer's disease, beta-amyloid excesses lead to the brain plaques that are thought to cause neural cell death. This study further strengthens the connection to Alzheimer's disease by showing that over-production of this protein can have pathological consequences in muscle as well as the brain.

The UCI researchers achieved this excess of the beta-amyloid precursor protein by cloning it in front of the DNA-control elements of the muscle creatine kinase gene, which was then subsequently injected into mice embryos. Using these gene elements allowed the human beta-amyloid precursor protein, from which beta-amyloid is derived, to be selectively overproduced in skeletal muscle of the mice. The team created two models of mice-one which expresses large amounts of the human protein, which led to more rapid and severe forms of myositis, and one expressing lesser amounts of the human protein, which exhibited a less virulent form of the disease.

In tests, LaFerla and Sugarman found that at 10 months, their transgenic mice began to show deficits in muscle performance, mirroring the age-related aspect of the human condition. Muscle biopsies revealed the pathological features of inclusion body myositis, such as muscle degeneration and inflammation, which is consistent with how the disease progresses in human muscle.

With their mouse model, LaFerla and his team are continuing their myositis research, testing whether exercise can delay the disease's onset, whether muscle injury makes it occur sooner or more severely, and whether enzyme inhibitor drugs that are being used in Alzheimer's research can control beta-amyloid amounts.

"These mouse models are opening up exciting new areas of research," LaFerla said. "Much of our understanding about inclusion body myositis has emerged from studying Alzheimer's disease, but there's no reason to believe that what we learn about myositis cannot be applied to Alzheimer's disease."

The National Institute of Aging supported the research, which is covered by a provisional patent. Assisting LaFerla and Sugarman in the study were Tritia Yamasaki, Salvatore Oddo, Julio Echegoyen, Mehrdad Jannatipour and Malcolm Leissring of UCI, and M. Paul Murphy and Todd Golde at the Mayo Clinic in Jacksonville, Fla.

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Amyloidosis, Overview

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Last Updated: October 4, 2004

Synonyms and related keywords: amyloid diseases, primary amyloidosis, secondary amyloidosis, myeloma-associated amyloidosis, familial amyloidosis, localized amyloidosis, senile amyloidosis, senile cardiac amyloidosis, light chain amyloidosis, AL, familial amyloid polyneuropathy, transport protein transthyretin, TTR, ATTR, systemic amyloidosis, A amyloidosis, AA, heavy chain amyloidosis, AH, beta₂-microglobulin amyloidosis, Aβ₂M, familial renal amyloidosis, apolipoprotein AI amyloidosis, AapoAI, fibrinogen amyloidosis, AFib, lysozyme amyloidosis, ALys, apolipoprotein AII amyloidosis, AapoAII, beta protein amyloid, Aβ, prion protein amyloidosis, APrP, cystatin C amyloidosis, ACys, gelsolin amyloidosis, AGel, atrial natriuretic factor amyloidosis, AANF, keratoepithelin amyloidosis, AKE, lactoferrin amyloidosis, ALac, calcitonin amyloidosis, ACal, islet amyloid polypeptide amyloidosis, AIAPP, prolactin amyloid, Apro, keratin amyloid, Aker

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DEFINITION OF AMYLOIDOSIS

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Amyloid diseases are secondary protein structure diseases in which insoluble protein fibrils accumulate extracellularly. Twenty different types of fibrils have been described in human amyloidosis, each with a different clinical picture. All types of tissue amyloid consist of a major fibrillar protein that defines the type of amyloid (approximately 90%) plus various minor components. All amyloid types share certain physical and pathologic properties, as follows:

- Amorphous eosinophilic appearance on light microscopy after hematoxylin and eosin staining (see [Image 1](#))
- Bright green fluorescence observed under polarized light after Congo red staining (see [Image 2](#))
- Regular fibrillar structure as observed by electron microscopy
- Beta pleated sheet structure as observed by x-ray diffraction
- Solubility in water and buffers of low ionic strength

For excellent patient education resources, visit eMedicine's [Brain and Nervous System Center](#). Also, see eMedicine's patient education article [Mad Cow Disease](#) and [Variant Creutzfeldt-Jakob Disease](#).

CLASSIFICATION SYSTEMS: HISTORICAL (CLINICAL BASED) & MODERN (BIOCHEMICAL BASED)

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Historical classification systems (clinical based)

Until the early 1970s, the idea of a single amyloid substance predominated. Various descriptive classification systems were proposed based on the organ distribution of amyloid deposits and clinical findings. Most classification systems included primary (ie, in the sense of idiopathic) amyloidosis, in which no associated clinical condition was identified, and secondary amyloidosis, ie, associated with chronic inflammatory conditions. Some classification systems included myeloma-associated, familial, and localized amyloidosis.

The modern era of amyloidosis classification began in the late 1960s with the development of methods to solubilize amyloid fibrils. These methods permitted chemical amyloid studies. Descriptive terms such as primary amyloidosis,

secondary amyloidosis, and others (eg, senile amyloidosis), which are not based on etiology, provide little useful information and are no longer recommended.

Modern amyloidosis classification (biochemical based)

Amyloid is now classified chemically. The amyloidoses are referred to with a capital A (for amyloid) followed by an abbreviation for the fibril protein. For example, in most cases formerly called primary amyloidosis and in myeloma-associated amyloidosis, the fibril protein is an immunoglobulin light chain or light chain fragment (abbreviated L); thus, patients with these amyloidoses are now said to have light chain amyloidosis (AL). Similarly, in most cases previously termed senile cardiac amyloidosis and in many cases previously termed familial amyloid polyneuropathy, the fibrils consist of the transport protein transthyretin (TTR); these diseases are now termed ATTR.

Twenty different fibril proteins are described in human amyloidosis; therefore, 20 different types of human amyloidosis are now evident. These different types are outlined in Table 1 and discussed individually below.

Table 1. Human Amyloidoses

Type	Fibril Protein	Main Clinical Settings
Systemic	Immunoglobulin light chains	Plasma cell disorders
	Transthyretin	Familial amyloidosis, senile cardiac amyloidosis
	A amyloidosis	Inflammation-associated amyloidosis, familial Mediterranean fever
	Beta ₂ -microglobulin	Dialysis-associated amyloidosis
	Immunoglobulin heavy chains	Systemic amyloidosis
Hereditary	Fibrinogen alpha chain	Familial systemic amyloidosis
	Apolipoprotein AI	Familial systemic amyloidosis
	Lysozyme	Familial systemic amyloidosis
	Beta protein precursor	Alzheimer syndrome, Down syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch)



Central nervous system	Prion protein	Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia
	Cystatin C	hereditary cerebral hemorrhage with amyloidosis (Icelandic)
Ocular	Gelsolin	Familial amyloidosis (Finnish)
	Lactoferrin	Familial corneal amyloidosis
	Keratoepithelin	Familial corneal dystrophies
Localized	Calcitonin	Medullary thyroid carcinoma
	Amylin*	Insulinoma, type 2 diabetes
	Atrial natriuretic factor amyloidosis	Isolated atrial amyloidosis
	Prolactin	Pituitary amyloid
	Keratin	Cutaneous amyloidosis
	Medin	Aortic amyloidosis in elderly people

* Islet amyloid polypeptide amyloidosis

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A amyloidosis

The precursor protein is a normal-sequence apo-SAA (serum amyloid A protein), which is an acute phase reactant that circulates in the serum bound to high-density lipoprotein.

In the clinical setting, chronic inflammation is associated with conditions such as the following:

- Leprosy
- Osteomyelitis
- Tuberculosis

- Rheumatoid arthritis
- Familial Mediterranean fever
- Hodgkin disease
- Renal cell carcinoma

Typical organs involved include the kidney, liver, and spleen. Worldwide, A amyloidosis (AA) is the most common systemic amyloidosis and was formerly termed secondary amyloidosis. Colchicine prevents renal failure from amyloid deposition in familial Mediterranean fever; no proven therapy exists in other settings. For details, see [Amyloidosis, AA \(Inflammatory\)](#).

Light chain amyloidosis

The precursor protein is a clonal immunoglobulin light chain or light chain fragment. AL is a monoclonal plasma cell disorder closely related to multiple myeloma; some patients fulfill diagnostic criteria for multiple myeloma. Typical organs involved include the heart, kidney, peripheral nerve, gastrointestinal tract, respiratory tract, and nearly any other organ. AL includes former designations of primary amyloidosis and myeloma-associated amyloidosis. Treatment mirrors that of multiple myeloma (ie, chemotherapy). Iododoxorubicin, a molecule that binds to and solubilizes amyloid fibrils, is undergoing clinical study. For more information, see [Amyloidosis, Immunoglobulin-Related](#).

Heavy chain amyloidosis

In a few cases, immunoglobulin chain amyloidosis fibrils contain only heavy chain sequences rather than light chain sequences, and the disease is termed heavy chain amyloidosis (AH) rather than AL. For more information, see [Amyloidosis, Immunoglobulin-Related](#).

Transthyretin amyloidosis

The precursor protein is the normal- or mutant-sequence TTR, a transport protein synthesized in the liver and choroid plexus. TTR is a tetramer of 4 identical subunits of 127 amino acids each. Normal-sequence TTR forms amyloid deposits in the cardiac ventricles of elderly people (ie, >70 y); this disease is also termed senile cardiac amyloidosis. The prevalence of TTR cardiac amyloidosis increases progressively with age, affecting 25% or more of the population older than 90 years. Normal-sequence TTR can be an incidental autopsy finding, or it can cause clinical symptoms (eg, heart failure, arrhythmias).

Point mutations in *TTR* increase the tendency of TTR to form amyloid. Amyloidogenic *TTR* mutations are inherited as an autosomal dominant disease with

variable penetrance. More than 60 amyloidogenic *TTR* mutations are known. The most prevalent *TTR* mutations are *TTR* Val30Met (common in Portugal, Japan, and Sweden), and *TTR* Val122Ile (carried by 3.9% of African Americans). Amyloidogenic *TTR* mutations cause deposits primarily in the peripheral nerves, heart, gastrointestinal tract, and vitreous.

Treatment for mutant-sequence amyloidogenic *TTR* is liver transplantation or supportive care. For normal-sequence amyloidogenic *TTR*, the treatment is supportive care. For details, see [Amyloidosis, Transthyretin-Related](#).

Beta₂-microglobulin amyloidosis

The precursor protein is a normal beta₂-microglobulin (β_2 M), which is the light chain component of the major histocompatibility complex. In the clinical setting, A β_2 M is associated with patients on dialysis and, rarely, patients with renal failure who are not on dialysis.

β_2 M is normally catabolized in the kidney. In patients with renal failure, the protein accumulates in the serum. Conventional dialysis membranes do not remove β_2 M; therefore, serum levels can reach as high as 30-60 times the reference range values in patients on hemodialysis. Typical organs involved include the carpal ligament and, possibly, the synovial membranes (leading to arthropathies and bone cysts) and the heart, gastrointestinal tract, liver, lungs, prostate, adrenals, and tongue.

Treatment includes renal transplantation, which may arrest amyloid progression. For details, see [Amyloidosis, Beta2M \(Dialysis-Related\)](#).

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Consider these diseases when a renal biopsy demonstrates amyloid deposition and when they diagnoses (rather than AL or AA) because the family history suggests an autosomal dominant. Again, the definitive diagnosis is made using immunohistologic staining of the biopsy material. Antibodies specific for the candidate amyloid precursor proteins. For details, see [Amyloidosis, Renal](#).

Apolipoprotein AI amyloidosis (ApoAI) is an autosomal dominant amyloidosis caused by a point mutation in the *apoAI* gene. Usually, this amyloidosis is a prominent renal amyloid. Some kindreds have neuropathy or cardiac disease. ApoAI (likely of normal sequence) also is the fibril precursor in amyloid plaques in the aortae of elderly people.

Fibrinogen amyloidosis (AFib) is an autosomal dominant amyloidosis caused by point mutation in the fibrinogen alpha chain gene.

Lysozyme amyloidosis (ALys) is an autosomal dominant amyloidosis caused by point mutation in the lysozyme gene.

Apolipoprotein AII amyloidosis (ApoAII) is an autosomal dominant amyloidosis caused by point mutations in the *apoAII* gene. The 2 kindreds described with this disorder have each carried a mutation in the stop codon, leading to production of an abnormally long protein.

CENTRAL NERVOUS SYSTEM AMYLOIDOSES AND OTHER LOCALIZED AMYLOIDOSES

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Central nervous system amyloidoses

Beta protein amyloid

The amyloid beta precursor protein (A β PP), which is a transmembrane glycoprotein, is the precursor protein in beta protein amyloid (A β). Three distinct clinical settings are as follows:

1. Alzheimer disease has a normal-sequence protein, except in some cases of familial Alzheimer disease, in which mutant beta protein is inherited in an autosomal dominant manner.
2. Down syndrome has a normal-sequence protein that forms amyloids in most patients by the third decade of life.
3. Hereditary cerebral hemorrhage with amyloidosis (HCHWA), Dutch type, is inherited in an autosomal dominant manner. The beta protein contains a point mutation. These patients present with cerebral hemorrhage followed by dementia.

Prion protein amyloidosis

The precursor protein in prion protein amyloidosis (APrP) is a prion protein, which is a plasma membrane glycoprotein. The etiology is either infectious (ie, kuru) or genetic (ie, Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker [GSS] syndrome, fatal familial insomnia [FFI]). The infectious prion protein, which induces a conformational change in a homologous protein encoded by a 19 kD chromosomal gene. Patients with CJD, GSS, and FFI carry autosomal dominant amyloidogenic mutations in the prion protein gene; therefore, the amyloidosis forms even in the absence of an external trigger.

Similar infectious animal disorders include scrapie in sheep and goats and bovine spongiform encephalitis (ie, mad cow disease).

Cystatin C amyloidosis

The precursor protein in cystatin C amyloidosis (ACys) is cystatin C, which is a cysteine protease inhibitor that contains a point mutation. This condition is clinically termed HCHWA, Icelandic type.

ACys is autosomal dominant. Clinical presentation includes multiple strokes and mental status beginning in the second or third decade of life. Many of the patients die by age 40 years. This is documented in a 7-generation pedigree in northwest Iceland. The pathogenesis is one of mutation that is widely distributed in tissues, but fibrils form only in the cerebral vessels; therefore, local factors must play a role in fibril formation.

Other localized amyloidoses

Gelsolin amyloidosis

The precursor protein in gelsolin amyloidosis (AGel) is the actin-modulating protein gelsolin. Amyloid fibrils include a gelsolin fragment that contains a point mutation. Two amyloidogenic gelsolin mutations are described. One example is Asp187Asn, which is endemic in southeast Finland.

Clinical characteristics include slowly progressive cranial neuropathies, distal peripheral neuropathy, and lattice corneal dystrophy.

Atrial natriuretic factor amyloidosis

The precursor protein is atrial natriuretic factor (ANF), a hormone controlling salt and water homeostasis and it is synthesized by the cardiac atria. Amyloid deposits are localized to the cardiac atria. This condition is highly prevalent in elderly people and generally is of little clinical significance. Atrial natriuretic factor amyloidosis (AANF) is most common in patients with long-standing congestive heart failure, presumably because of persistent ANF production. No relation exists to the amyloidosis that involves the cardiac ventricles (ie, AL, ATTR).

Keratoepithelin amyloidosis and lactoferrin amyloidosis

Point mutations occur in a gene termed *BIGH3*, which encodes keratoepithelin and leads to autosomal dominant corneal dystrophies characterized by the accumulation of corneal amyloid. Some *BIGH3* mutations cause amyloid deposits, and others cause nonfibrillar corneal deposits. Another protein, lactoferrin, is also reported as the major fibril protein in familial subepithelial corneal amyloidosis. The relationship between keratoepithelin and lactoferrin in familial corneal amyloidosis is not yet clear.

Calcitonin amyloid

In calcitonin amyloid (ACal), the precursor protein is calcitonin, a calcium regulatory hormone synthesized by the thyroid. Patients with medullary carcinoma of the thyroid may develop local amyloid deposition in the tumors, consisting of normal-sequence procalcitonin (ACal). The pathogenesis is increased local calcitonin production, leading to a sufficiently high local concentration of the peptide and causing polymerization and fibril formation.

Islet amyloid polypeptide amyloidosis

In islet amyloid polypeptide amyloidosis (AIAPP), the precursor protein is an islet amyloid polypeptide (IAPP), also known as amylin. IAPP is a protein secreted by the islet beta cells that are stored with insulin in the secretory granules and released in concert with insulin. Normally, IAPP modulate activity in skeletal muscle. IAPP amyloid is found in insulinomas and in the pancreas of many with diabetes mellitus type 2.

Prolactin amyloid

In prolactin amyloid (Apro), prolactin or prolactin fragments are found in the pituitary amyloid. This condition is often observed in elderly people and has also been reported in an amyloidoma in association with a prolactin-producing pituitary tumor.

Keratin amyloid

Some forms of cutaneous amyloid react with antikeratin antibodies. The identity of the fibrils is chemically confirmed in keratin amyloid (Aker).

Medin amyloid

Aortic medial amyloid occurs in most people older than 60 years. Medin amyloid (AMed) is derived from a proteolytic fragment of lactadherin, a glycoprotein expressed by mammary epithelium.

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All types of amyloid deposits contain not only the major fibrillar component (solubility in water, low ionic strength) but also nonfibrillar components that are soluble in conventional ionic strength. The role of the minor components in amyloid deposition is not clear. These components do not have to be absolutely required for fibril formation, but they may enhance fibril formation or stabilize formed fibrils.

The nonfibrillar components, contained in all types of amyloid, include the following:

- Pentagonal component
 - Pentagonal (P) component comprises approximately 5% of the total protein in amyloid deposits. This component is derived from the circulating serum amyloid P (SAP) component, which behaves as an acute phase reactant. The P component is one of the pentraxin proteins, with homology to C-reactive protein. In experimental animals, amyloid deposition is slowed without the P component.
 - Radiolabeled material homes to amyloid deposits; therefore, this component can be used in amyloid scans to localize and quantify amyloidosis and to monitor therapy response. Radiolabeled P component scanning has proven clinically useful in England, where this technology was developed, but it is available in only a few centers worldwide.

- Apolipoprotein E
 - Apolipoprotein E (apoE) is found in all types of amyloid deposits.
 - One allele, ApoE4, increases the risk for beta protein deposition, which is associated with Alzheimer disease. ApoE4 as a risk factor for other forms of amyloidosis is controversial.
 - The role of apoE in amyloid formation is not known.
- Heparan sulfate proteoglycans
 - These proteoglycans are basement membrane components intimately associated with some types of tissue amyloid deposits.
 - Heparan sulfate proteoglycans have an unknown role in amyloidogenesis.
 - Compounds that bind to heparan sulfate proteoglycans (eg, anionic sulfonates) decrease deposition in murine models of AA and have been suggested as potential therapeutic agents.
- Other components found in some types of amyloid include complement components, proteoglycans, and membrane constituents.

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Amyloid protein structures

In all forms of amyloidosis, the cell secretes the precursor protein in a soluble form that becomes insoluble at some tissue site, compromising organ function. All the amyloid precursor proteins are relatively small (ie, molecular weights 4000-25,000) and do not share any amino acid sequence homology. The secondary protein structures of most soluble precursor proteins (except for SA β and chromosomal prion protein [Prp^C]) have substantial beta pleated sheet structure, while extensive alpha helix structure occurs in all of the deposited fibrils.

In some cases, hereditary abnormalities (primarily point mutations) in the precursor proteins are present (eg, lysozyme, fibrinogen, cystatin C, gelsolin). In other cases, fibrils form from normal molecules (eg, AL, β_2 M). In other cases, normal-sequence proteins can form amyloid, but mutations accelerate the process (eg, TTR, beta protein precursor).

Deposition location

In localized amyloidoses, the deposits form close to the precursor synthesis site; however, in systemic amyloidoses, the deposits may form either locally or at a distance from the precursor-producing site.

Amyloid deposits primarily are extracellular, but reports exist of fibrillar structures within macrophages and plasma cells.

Proteolysis and protein fragments

In some types of amyloidosis (eg, always in AA, often in AL, ATTR), the amyloid precursors undergo proteolysis, which may enhance folding into an amyloidogenic structural intermediate. Also, some amyloidoses may have a normal proteolytic process that is disturbed, yielding a high concentration of amyloidogenic intermediate. The factors that lead to different organ tropism for the different amyloid types are unknown.

Whether the proteolysis occurs before or after tissue deposition is unclear in patients in whom amyloid fragments are observed in tissue deposits. In some types of amyloid (eg, AL, A β , ATTR), nonfibrillar forms of the same molecules can accumulate before fibril formation; thus, nonfibrillar deposits, in some cases, may represent intermediate deposition.

APPROACH TO DIAGNOSING AMYLOIDOSIS

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Pathologic diagnosis (Congo red staining and immunohistochemistry)

Amyloidosis is diagnosed when Congo red-binding material is demonstrated in a biopsy specimen. Because different types of amyloidosis require different approaches to treatment, determining whether a patient has a diagnosis of amyloidosis is no longer adequate. A clinical situation may suggest amyloidosis, but the diagnosis generally must be confirmed by immunostaining a biopsy specimen. Antibodies against the major amyloid fibril precursors are commercially available. For example, AL and A β ₂M can present as carpal tunnel syndrome or gastrointestinal amyloidosis, but each has a different etiology and requires a different treatment approach.

Similarly, determining whether the amyloid is of the AL or ATTR type is often difficult in patients with cardiac amyloidosis, because the clinical picture is usually similar. Without immunostaining to identify the type of deposited protein, an incorrect diagnosis can lead to ineffective and, perhaps, harmful treatment. Be wary of drawing diagnostic conclusions from indirect tests (eg, monoclonal serum proteins); the results of these presumptive diagnostic tests can be misleading; for example, monoclonal immunoglobulins are common in patients older than 70 years, but the most common form of cardiac amyloidosis is derived from TTR.

Diagnosis by subcutaneous fat aspiration

For many years, rectal biopsy was the first procedure of choice. An important clinical advance was the recognition that the capillaries in the subcutaneous fat are often involved in patients with systemic amyloidosis and can often provide sufficient tissue for the diagnosis of amyloid, immunostaining or, in some cases, amino acid sequence analysis; thus, biopsy of the organ with the most severe clinical involvement is often unnecessary.

For example, in cardiac amyloidosis, the definitive diagnosis of the type of amyloid can be made on an endomyocardial biopsy specimen, with Congo red and immunologic staining of the tissue sample. Alternatively, when noninvasive testing suggests cardiac amyloidosis, a specific diagnosis is often made by studying a subcutaneous fat aspiration instead of endomyocardial biopsy, thereby avoiding an invasive procedure.

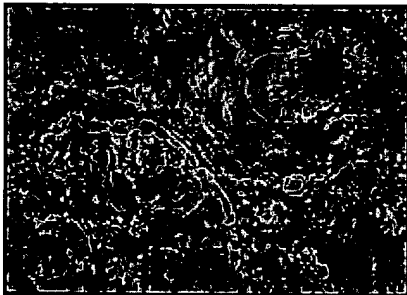
Organ biopsies

When the subcutaneous fat aspiration biopsy does not provide information to reach a firm diagnosis, biopsies can be obtained from other organs. In addition, an advantage to performing a biopsy of an involved organ (eg, kidney, heart) is that it definitively establishes a cause-and-effect relationship between the organ dysfunction and amyloid deposition.

Other sites that are often sampled include the salivary glands, stomach, and bone marrow.

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Caption: Picture 1. Amyloidosis overview. Amorphous eosinophilic interstitial amyloid observed on a renal biopsy.



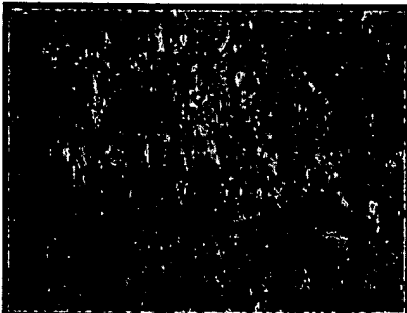
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Caption: Picture 2. Amyloidosis overview. Congo red staining of a cardiac biopsy specimen containing amyloid, viewed under polarized light.



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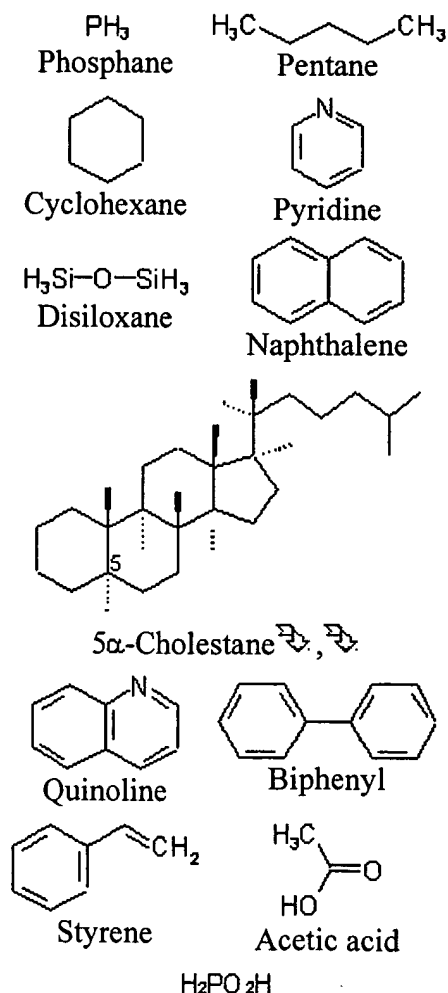
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General Principles of Organic Nomenclature

R-1.0 Introduction

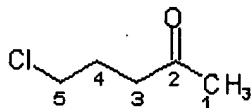
Systematic naming of an organic compound generally requires the identification and naming of a parent structure. This name may then be modified by prefixes, infixes, and, in the case of a parent hydride, suffixes, which convey precisely the structural changes required to generate the actual compound from the parent structure.

Most commonly, a *parent structure* is a parent hydride, i.e., a structure containing, besides hydrogen, either a single atom of an element, for example, phosphane; a number of atom (alike or different) linked together to form an unbranched chain, for example, cyclohexane, pyridine, naphthalene, and quinoline. It is sometimes convenient to employ parent hydrides, of more complex structure such as ring assemblies or ring/chain systems, for example, biphenyl, styrene, ferrocene, and cyclophanes, and to include structures with implied stereochemistry (stereoparents), for example, 5-cholestane . Rules for naming parent hydrides are given in R-2; in addition, a special class of parent structures termed functional parents, for example, phosphinic acid, is considered in R-3.3. Examples of parent structures are shown below:



Phosphinic acid

In order to generate the parent structure from a molecule to be named, various formal operations must be carried out. For example, in naming the structure below,



the parent hydride "pentane" is formally derived by replacing the oxygen and chlorine atoms by the appropriate number of hydrogen atoms. For constructing a name, this formal operation is reversed; the prefix "chloro-" and the suffix "-one" indicating substitution of hydrogen atoms of pentane are attached to the parent hydride name, giving the name *5-chloropentan-2-one*. Prefixes and suffixes can represent a number of different types of formal operations on the parent structure. These are defined in R-1.2. Frequently, the prefix or suffix denotes the attachment of a characteristic group, for example, "oxo-" or "-one" for =O; lists of such affixes are given in R-3.2. A prefix may describe a group which is derived from a parent hydride, for example, pentan-1-yl or pentyl for $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—}$ (from pentane); such prefixes are described in R-2.5.

The substitutive operation, described in R-1.2.1, is the operation used most extensively in organic nomenclature. Indeed, the comprehensive nomenclature system based largely on the application of this operation to parent structures is, for convenience, termed "substitutive nomenclature", although this system also involves many of the other types of operations described in R-1.2. Examples of this and other nomenclature operations are shown in Table 1.

In constructing the names described in R-1.2.3.3.2 (formerly called "radicofunctional names"), the characteristic group of the compound is expressed as a functional class name, and is usually cited as a separate word rather than as a suffix. In these recommendations, however, names obtained by a substitutive operation are preferred.

The replacement operation can be used for naming organic compounds in which skeletal atoms of a parent structure are replaced by other skeletal atoms, or in which oxygen atom and/or hydroxy groups of characteristic groups are replaced by other atoms or groups.

It is very important to recognize that, in general, the rules of organic nomenclature are written in terms of classical valence bonding and do not imply electronic configurations of any kind.

Examples of naming structures in several ways are shown in Table 1.

Full details of the way in which parent names may be combined with appropriate prefixes and suffixes are given in R-4 (Name Construction); rules for selection of a unique systematic name, if required, will be described in a separate document. Methods for the specification of stereochemistry are given in R-7 and those for denoting isotopic modification are described in R-8.

See Also:

R-1.1 Bonding Number

R-1.2 Nomenclature Operations

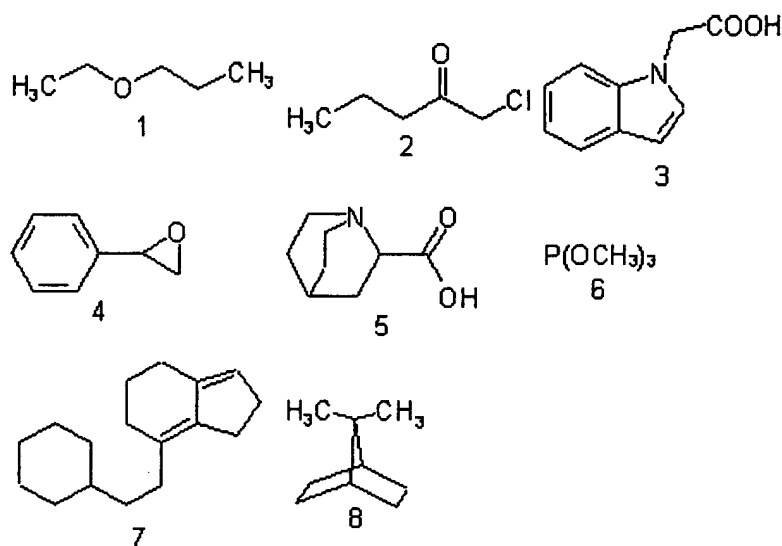
R-1.3 Indicated Hydrogen

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Table 1 Examples of nomenclature operations

Structure	Parent structure (Class Name)	Operation	Name	Reference
1	Propane(ether)	substitutive functional class	1-Ethoxypropane Ethyl propyl ether	R-1.2.1 R-1.2.3.3.2
2	Pentane(ketone)	substitutive functional class	1-Chloropentan-2-one Chloromethyl propyl ketone	R-1.2.1 R-1.2.3.3.2
3	Acetic acid Indole and Acetic acid	substitutive conjunctive	1 <i>H</i> -Indol-1-ylacetic acid 1 <i>H</i> -Indole-1-acetic acid	R-1.2.1 R-1.2.4.1
4	Styrene (oxide) Oxirane	additive substitutive	Styrene oxide 2-Phenyloxirane	R-1.2.3.3 R-1.2.1
5	Quinuclidine Bicyclooctane	substitutive replacement substitutive	Quinuclidine-2-carboxylic acid 1-Azabicyclo[2.2.2] octane-2- carboxylic acid	R-1.2.1 R-1.2.2.1 R-1.2.1
6	(phosphite) Phosphane	functional class substitutive coordination (additive)	Trimethyl phosphite Trimethoxyphosphane Trimethoxophosphorus	R-1.2.3.3.2 R-1.2.1 R-1.2.3.1
7	Gonane Indene	ring cleavage subtractive substitutive additive	9,10-Secogona-8(14),13(17)- diene 7-(2-Cyclohexylethyl)-2,4,5,6- tetrahydro-1 <i>H</i> -indene	R-1.2.6.2 R-1.2.5.2 R-1.2.1 R-1.2.3.1
8	Bornane Bicycloheptane	subtractive substitutive	10-Norbornane 7,7-Dimethylbicyclo- [2.2.1]heptane	R-1.2.5.1 R-1.2.1

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